

Mechanisms Underlying the Responses of Normal and Cancer Stem Cells to Environmental and Therapeutic Insults

Grant Award Details

Mechanisms Underlying the Responses of Normal and Cancer Stem Cells to Environmental and Therapeutic Insults

Grant Type: New Faculty II

Grant Number: RN2-00934

Project Objective: The original goal was to use mouse leukemia models to understand how deregulation of apoptosis and DNA repair within stem cells contributes to cancer development. Over time, the goals evolved to focus on molecular mechanisms through which normal and aged HSCs respond to various types of stresses (genotoxic, metabolic, replicative), and how those changes impact function and behavior.

Investigator:

Name:	Emmanuelle Passegue
Institution:	University of California, San Francisco
Type:	PI

Disease Focus: Blood Cancer, Cancer, Trauma

Award Value: \$2,124,488

Status: Closed

Progress Reports

Reporting Period: Year 1

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Reporting Period: Year 5

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Grant Application Details

Application Title: Mechanisms Underlying the Responses of Normal and Cancer Stem Cells to Environmental and Therapeutic Insults

Public Abstract: Adult stem cells play an essential role in the maintenance of tissue homeostasis. Environmental and therapeutic insults leading to DNA damage dramatically impact stem cell functions and can lead to organ failure or cancer development. Yet little is known about the mechanisms by which adult stem cells respond to such insults by repairing their damaged DNA and resuming normal cellular functions. The blood (hematopoietic) system provides a unique experimental model to investigate the behaviors of specific cell populations. Our objective is to use defined subsets of mouse hematopoietic stem cells (HSCs) and myeloid progenitor cells to investigate how they respond to environmental and therapeutic insults by either repairing damaged DNA and restoring normal functions; accumulating DNA damage and developing cancer; or undergoing programmed cell death (apoptosis) and leading to organ failure. These findings will provide new insights into the fundamental mechanisms that regulate stem cell functions in normal tissues, and a better understanding of their deregulation during cancer development. Such information will identify molecular targets to prevent therapy-related organ damage or secondary cancers. These are severe complications associated with current cancer treatments and are among the leading causes of death worldwide. Originally discovered in blood cancers (leukemia), cancer stem cells (CSCs) have now been recognized in a variety of solid tumors. CSCs represent a subset of the tumor population that has stem cell-like characteristics and the capacity for self-renewal. CSCs result from the transformation of either stem or progenitor cells, which then generate the bulk of the cancer cells. Recent evidence indicates that CSCs are not efficiently killed by current therapies and that CSC persistence could be responsible for disease maintenance and cancer recurrence. Developing interventions that will specifically target CSCs is, therefore, an appealing strategy for improving cancer treatment, which is dependent on understanding how they escape normal regulatory mechanisms and become malignant. Few mouse models of human cancer are currently available in which the CSC population has been identified and purified. This is an essential prerequisite for identifying pathways and molecules amenable to interventional therapies in humans. We have previously developed a mouse model of human leukemia in which we have identified the CSC population as arising from the HSC compartment. We will use this model to understand how deregulations in apoptosis and DNA repair processes contribute to CSC formation and function during disease development. These results will provide new insights into the pathways that distinguish CSCs from normal stem cells and identify ways to prevent their transformation. Such information will be used to design novel and much-needed therapies that will specifically target CSCs while sparing normal stem cells.

Statement of Benefit to California:

This application investigates how environmental and therapeutic insults leading to DNA damage impact stem cell functions and can lead to organ failure or cancer development. The approach is to study how specific population of blood (hematopoietic) stem, progenitor, and mature cells respond to DNA damaging agents and chose a specific cellular outcome. Such information could identify molecular pathways that are available for interventional therapies to prevent end-organ damage in patients who are treated for a primary cancer and reduce the risk of a subsequent therapy-induced cancer. These are severe complications associated with current mutagenic cancer treatments (radiation or chemotherapeutic agents) that comprise a substantial public health problem in California and in the rest of the developed world. The hematopoietic system is the first to fail following cancer treatment and the formation of therapy-related blood cancer (leukemia) is a common event. The development of novel approaches to prevent therapy-related leukemia will, therefore, directly benefit the health of the Californian population regardless of the type of primary cancer. This application also investigates a novel paradigm in cancer research, namely the role of cancer stem cells (CSCs) in the initiation, progression and maintenance of human cancer. The approach is to study how dysregulations in important cancer-associated pathways (apoptosis and DNA repair processes) contribute to CSC aberrant properties using one of the few established mouse model of human cancer where the CSC population has already been identified. Leukemia, the disease type investigated in this application, has been the subject of many landmark discoveries of basic principles in cancer research that have then been shown to be applicable to a broad range of other cancer types. Accordingly, this research should benefit the people of California in at least two ways. First, the information gained about the properties of CSCs should improve the ability of our physicians and scientists to design, develop and evaluate the efficacy of innovative therapies to target these rare disease-initiating cells for death. This would place Californian cancer research at the forefront of translational science. Second, an average of 11.55 out of 100,000 Californian inhabitants are diagnosed with primary leukemia each year. Thus, in California, leukemia occurs at approximately the same frequency as brain, liver and endocrine cancers. As is true for many types of cancer, most cases of leukemia occur in older adults. At this time, the only treatment that can cure leukemia is allogeneic stem cell transplantation, which is a high-risk and expensive procedure that is most successful in younger patients. The development of novel and safe curative therapies for leukemia would, therefore, particularly benefit the health of our senior population and the economy of the state of California by realizing savings in the healthcare sector.

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